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WO 2004/035819 A3

(54) Title: OLIGONUCLEOTIDES USEFUL FOR DETECTING AND ANALYZING NUCLEIC ACIDS OF INTEREST

(57) Abstract: The invention features improved non-naturally occurring nucleic acids with higher melting temperature than control nucleic acid with 2' deoxynukleotides, and methods for expression profiling of mRNAs, identifying and profiling of particular mRNA splice variants, and detecting mutations, deletions, or duplications of particular exons or other splice variants, e.g., alterations associated with a disease such as cancer, in a nucleic acid sample, e.g., a biological sample or a patient sample.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 03/00715

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68 C07H21/00 C12N15/11

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12Q C07H C12N G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 81632 A (BALABAN DAVID ;AFFYMETRIX INC (US)) 1 November 2001 (2001-11-01) page 33, line 14 - line 18 page 38, line 17 - line 19; claims --- -/--	1-156, 160-184

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 June 2004	19 JUL 2004

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 03/00715

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 14226 A (WENGEL JESPER ;EXIQON A S (DK); NIELSEN POUL (DK)) 25 March 1999 (1999-03-25) page 60, line 1 - line 9 page 65, line 9 - line 16	1-112, 115-138, 141,142, 145,159, 166-179, 182-184
Y		113,114, 139,140, 143,144, 148, 160-165, 180,181

Y	WO 02 061387 A (JAKOBSEN MOGENS HASTEEN ;EXIQON AS (DK); KONGSBAK LARS (DK)) 8 August 2002 (2002-08-08) page 4, line 18 - line 21 page 5, line 18 - line 20	113,114, 139,140, 143,144, 148, 160-165, 180,181

A	DWAINE A. BRAASCH ET AL: "Locked nucleic acid (LNA): fine-tuning the recognition of DNA and RNA" CHEMISTRY & BIOLOGY, vol. 8, 2001, pages 1-7, XP002285000 the whole document	1-184

P,X	NIELS TOLSTRUP ET AL: "OligoDesign: optimal design of LNA (locked nucleic acid) oligonucleotide capture probes for gene expression profiling" NUCLEIC ACIDS RESEARCH, vol. 31, no. 13, 2003, pages 3758-3762, XP002285001 the whole document	1-184

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 03/00715

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-6,16-17,19-21
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-6,16-17,19-21

Present claims 1-6, 16-17 and dependent claims relate to a compounds defined either by these two parameters:
P1: having a melting temperature at least 3 degrees C higher than that of a corresponding control nucleic acid, or
P2: maving a capture efficiency that is at least 10% greater than that of a corresponding control nucleic acid .
The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to any non-naturally occurring nucleic acid.

Moreover, claims 19-21-depending on claims 1-9 can be considered unclear since claims 1.-9 relates to nucleic acids with two capture regions, whereas nucleic acids of claims 19-21 explicitly are limited to be capable of hybridizing to either only one intron or exon. The nucleic acids of claims 19-21 are interpreted as being capable of hybridizing to one exon and one intron region.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/DK 03/00715

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0181632 A	01-11-2001	AU 5723901 A	07-11-2001
		CA 2406402 A1	01-11-2001
		EP 1285089 A1	26-02-2003
		JP 2003530894 T	21-10-2003
		WO 0181632 A1	01-11-2001
WO 9914226 A	25-03-1999	AU 9063398 A	05-04-1999
		CA 2303299 A1	25-03-1999
		CN 1279687 T	10-01-2001
		WO 9914226 A2	25-03-1999
		EP 1015469 A2	05-07-2000
		JP 2002521310 T	16-07-2002
		NZ 503765 A	26-04-2002
		US 2003134808 A1	17-07-2003
		US 2002068708 A1	06-06-2002
		US 2003144231 A1	31-07-2003
		US 6670461 B1	30-12-2003
WO 02061387 A	08-08-2002	EP 1337826 A2	27-08-2003
		WO 02061387 A2	08-08-2002
		WO 02097398 A2	05-12-2002
		US 2002187485 A1	12-12-2002
		US 2003152927 A1	14-08-2003